Atherosclerosis is a disease of chronic inflammation of large arteries with intermittent acute exacerbations that are associated with clinical events. Leukocytes migrate into the arterial wall after adhering to and migrating through the endothelium. The vascular endothelium normally does not attract adherence of leukocytes or of platelets and, thus, basally is anti-inflammatory and antithrombogenic. “Dysfunctional” endothelium, which is associated with the presence of traditional cardiovascular risk factors such as hypertension, hypercholesterolemia and diabetes mellitus, on the other hand, may attract leukocyte adherence and be prothrombogenic for multiple reasons, including enhanced platelet adherence. Dysfunction of the endothelium also is characterized by the loss of its normal role as a vasodilator, a function that is mediated to an important extent by the generation of NO by endothelial NO synthase. In dysfunctional endothelium, NO is degraded by reactive oxygen species (ROS) from several sources, including prominently NADPH oxides activated by Ang II through the AT1R and by hyperlipidemia and insulin resistance and hyperglycemia.

Formation of atherosclerotic lesions is a characteristic consequence of endothelial dysfunction in large arteries. Moreover, some evidence exists that the endothelial metabolic disequilibrium with excessive ROS production and decreased NO availability associated with large artery disease may also extend to the microvasculature and may reflect a systemic endothelial abnormality. The coexistence of arterial disease and microvasculopathy in diabetes mellitus is generally appreciated, and important roles for Ang II and AT1R in the process have been established, especially in the renal circulation. Hypercholesterolemia is associated with adherence of leukocytes and platelets as well as with NADPH oxidase–dependent oxidative stress in the microvasculature. Similarly, Ang II infusion causes microvascular leukocyte and platelet adherence.

Petnehazy et al recently have shown that the AT1R inhibitor losartan attenuates the prothrombotic (platelet adhesion) and proinflammatory (leukocyte adhesion and migration into tissue) effects of hypercholesterolemia in the microvasculature of mice. However, the experimental approach did not permit distinguishing between effects of the AT1R blocker on receptors on platelets or leukocytes versus those on endothelium. Moreover, the mechanistic questions are complicated further by observations that certain AT1R inhibitors, including losartan (and its metabolite EXP 3179) and valsartan, enhance the anti-inflammatory and antithrombotic functions of platelets and endothelium by non-AT1R–specific increases of platelet or endothelial NO or inhibition of cyclooxygenase-2 expression and activity to form thromboxane A2 and prostaglandin F2α. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Petnehazy et al describe the use of an innovative genetic approach to gain insights into the problem of identifying the cell types involved in mediating the AT1R-mediated responses in the microvasculature. They exploited the availability of the AT1aR−/− mouse and created chimeras with AT1aR−/− leukocytes and platelets (AT1aCh) by transplanting bone marrow of the knockout mouse into irradiated congenic wild-type (WT) animals. Thus, they developed hypercholesterolemic WT, WT with WT marrow transplant as control, AT1aCh, and AT1aR−/− mice and compared microvascular adherence of leukocytes and of infused platelets from WT to WT, WTCh to WTCh, AT1aR−/− to AT1aR−/−, and AT1aCh to AT1aCh mice. A major message from these experiments was that the adhesion of leukocytes to venular endothelium (and subsequent tissue migration) in the microvasculature of hypercholesterolemic mice was dependent on AT1aR on the white blood cells themselves, whereas platelet adherence was dependent on the endothelial and not the platelet AT1aR. The underlying mechanisms in each instance are incompletely understood. Ang II activation of the AT1R induces oxidative stress in neutrophils, which could facilitate binding to endothelial cells directly or indirectly by modulating endothelial adhesion molecules, possibly through neutrophil-generated ROS. Alternatively, endothelial...
cell–leukocyte adhesion could be modulated by hypercholes-
terolemia-induced T-cell production of interferon-γ, as has
been demonstrated previously.16 Hypercholesterolemia-
induced endothelial redox stress mediated through the AT1R
could mediate adhesiveness for platelets through to be
defined mechanisms.

These results are important in several contexts. The observa-
tion that hypercholesterolemia induces inflammatory and
potentially thrombogenic responses in the venous microvas-
culature strengthens the conceptual view that systemic met-
abolic or lifestyle-mediated conditions that traditionally have
been viewed as causing diseases primarily of large arteries
may result in generalized vasculopathies. This view could
result in reassessment of the potential roles of microvascular
dysfunction and the attendant inflammation in concert
with platelet adherence and activation in mediating nonvascular
parenchymal cell abnormalities, such as, for example, cardio-
myopathies in atherosclerosis and diabetes mellitus. Addi-
tionally, the novel observation of the role of the AT1R on
leukocytes in inducing microvascular inflammation in hyper-
cholesterolemia is provocative and unexpected and should
stimulate further investigation into its role in these cells and
how it drives interaction with the endothelium. Ang II has
been shown strongly to stimulate inflammatory responses
in small renal and cardiac vessels in a manner that was not
related to blood pressure, as inferred from experiments in
transgenic mice with a constitutively activated renin angiotensin
system.20 AT1R expression is increased in the atherosclerotic
aorta in hypercholesterolemic models and in cultured vascular
smooth muscle cells when exposed to low-density lipopro-
tin.11,12 A linkage between hypercholesterolemia and activation
of the renin angiotensin system likely involves inflammatory
cytokines and their stimulation of vascular oxidative stress and
enhanced AT1R expression.23 Thus, hypercholesterolemia and
potentially other inflammatory states may induce feed-forward
mechanisms in which increasing AT1R expression creates a
progressively important role for the renin angiotensin system in
maintaining the inflammatory process. The unique observations
in this article provide a new foundation for postulating a more
expansive role of the AT1R in vascular disease than has been
considered previously.

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